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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,645	11/13/2001	Menzo Jans Emco Havenga	5006.1US	4875

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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,645	HAVENGA ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28 and 48-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *54-61* is/are allowed.

6)☒ Claim(s) *28 and 48-49 and 51-53* is/are rejected.

7)☒ Claim(s) *50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 3/22/04. Claims 1-27 and 29-47 have been cancelled. Claims 49-61 have been added. Claim 28 has been amended. Claims 28 and 48-61 are pending.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Information Disclosure Statement

An IDS filed 3/22/04 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is**

maintained for reasons of record in the office action mailed 12/24/03 and restated below based upon applicants' amendment.

Applicants claim a method for delivering a nucleic acid of interest comprising administering recombinant adenovirus fiber protein comprised of at least one protein fragment of an adenovirus serotype C and at least a knob domain of a fiber protein of a second adenovirus serotype. The recombinant adenovirus has the functional limitation of tropism for mesenchymal stem cells.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

Applicants recite a large genus of fibers comprised of at least one protein fragment of a subgroup C adenovirus and at least a knob domain from a second adenovirus serotype. The instant specification teaches construction of recombinant adenovirus using a vector, pBr/Ad.BamRΔFib, deleted of the entire adenovirus 5 (ad5) fiber sequences (see e.g. paragraph 0091). Fiber sequences are amplified from adenovirus 16, 35, 40-S and 51 and inserted into pBr/Ad.BamRΔFib. However, there is no actual reduction to practice or clear depiction of ad5 protein fragments structure or properties are required for generation of the recited recombinant adenovirus fiber proteins. Neither applicant nor the prior art provide a correlation between the structure of

any protein fragment and the ability to form a chimeric fiber that can function to determine tropism. In an unpredictable art, the disclosure of no species would represent to the skilled artisan a lack of a representative number of species sufficient to show applicants were in possession of claimed genus. Given the diversity of protein fragments of an adenovirus serotype of subgroup C and the lack of written disclosure of the structural characteristics, and the lack of written disclosure of the functional characteristics required of the fragment for fiber production in a chimeric fiber, it is concluded that applicant was not in possession of their invention.

Response to Amendment-lack of written description

Applicants traverse the claim rejections under 35 U.S.C. 112, written description, on pages 6-7 of the amendment filed 3/22/04. Applicants argue that the instant specification combined with the knowledge of a person of ordinary skill in the art provides a written description of the correlation between the structure of a fragment of a fiber protein and tropism. Applicants specifically reference Krasnykh et al, which teaches the generation of a recombinant fiber protein wherein the knob domain from Ad3 replaces the knob domain of Ad5. It is said that the same reasoning could be used to delineate the structures and properties of the Ad5 fiber and recognize that the length and source of the stem region may vary without departing from the invention.

Applicant's arguments filed 3/22/04 have been fully considered but they are not persuasive. The instant specification hasn't provided a structural/ functional basis for the skilled artisan to envision the broad genus of protein fragments that can form a functional fiber in conjunction with the knob domain of a second adenovirus to direct infection of

mesenchymal stem cells. Given the large genus of protein fragments of an adenovirus serotype of subgroup C, it would require experimentation to determine which of the resulting chimeric proteins comprising the protein fragment with at least a knob domain of a second adenovirus serotype would function to form a fiber protein with tropism for mesenchymal cells. The specification does not reduce to practice the ability to determine which protein fragments of Ad5 will function with the knob domain of another adenoviral strain to form a functional fiber that can infect mesenchymal stem cells. The instant specification describes the substitution of the entire Ad5 fiber with that of a second adenovirus serotype such as 16, 35, 40-S and 51. Applicants reference Krasnykh et al, which demonstrates that a single chimera comprised of the tail and shaft of Ad5 and the knob domain of Ad3 forms a functional fiber. However, this single example does not provide teachings that can be extrapolated to any protein fragment of an adenovirus of serotype C such that one can envision embodiments of the claimed invention that meet the functional limitations of the claims. The ability to determine *a priori* which protein fragment will function to mediate infection of mesenchymal cells is highly unpredictable. Therefore, the claims lack sufficient written description to envision a chimeric fiber comprising any protein fragment and a knob domain from a second serotype.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28, 48-49 and 51-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering to mesenchymal cells *in*

vitro a recombinant adenovirus comprising a nucleic acid of interest and a fiber protein of a second adenovirus with tropism for mesenchymal stem cells, does not reasonably provide enablement for administering the recombinant adenovirus *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 12/24/03 and is restated below based upon applicants' amendment. The rejection has been extended to newly added claims 49 and 51-53.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites a method for delivering a nucleic acid of interest to mesenchymal stem cells (MSC) using a recombinant adenovirus with tropism for MSC obtained from adenovirus serotypes 16, 32, 35, 40-S or 51. This invention requires a complex combination of molecular cloning in combination with viral and cell culture techniques to generate the recombinant adenovirus in combination with clinical techniques form administration of the particles to subjects.

2) Scope of the invention. The invention recites administration of the recombinant adenovirus to mesenchymal stem cells to deliver a nucleic acid of interest. The only recited *in vivo* uses are for gene therapy.

3) Number of working examples and guidance. The instant specification teaches means of constructing and purifying rAd comprised of chimeric coat proteins. Furthermore, the specification teaches transduction of human mesenchymal stem cells in culture. Applicants teach on page 2, paragraph 0003 that the invention is designed for gene therapy and some prospective applications are described on page 9, paragraph 0035-0037. However, the specification fails to demonstrate any examples or guidance for deliverance of nucleic acids to cells *in vivo*.

4) State of the art. There has been much interest in the development of viruses that transduce therapeutic genes into target tissues. However, the lack of established protocols and positive results has hampered the use of such inventions. Therefore, the art must be considered to be poorly developed.

5) Unpredictability of the art. Adenoviral vector use for gene therapy is hindered by the transient nature of the transgene expression coupled with host immune responses. Approaches to prolong transgene expression by multiple injections of adenovirus or to increase transgene expression cause have proven futile in the face of these host immune responses to the recombinant adenoviral vector (Kmiec, American Scientist p 243 and Anderson, Nature p. 28). Use of adenovirus is thwarted by the humoral immune responses as taught by Verma and Somia Nature p. 241; "Unfortunately for gene therapy, most of the human population will probably have antibodies to adenovirus from previous infection with the naturally occurring virus" (Verma and

Somia, p 241). And "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene (p. 4, column 2).

The unpredictability of use of the instantly claimed invention in humans is accentuated by the lack of methods or processes disclosed in the specification. Many parameters must be addressed for *in vivo* use such as tumor cell selectivity in humans, lack of toxicity to normal tissues, and the effect of the antiviral immune response as well as doses to be administered, dose schedules etc. For example, what level of expression is necessary to achieve therapeutic affects without toxicity to normal cells that results from leaky expression of the viral gene required for replication? The method of delivery presents an obstacle for adenovirus use. "While reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle positioned in a tumour deposit. This strategy achieves a relatively low efficiency of gene delivery, which is confined to tumour cells immediately adjacent to the needle track. Plasmids or viral particles delivered in this way do not permeate freely through the interstitial fluid bathing the tumour." (Russell, European Journal of Cancer p 1165, column 2).

6) Amount of Experimentation Required. The invention recites use of a rAd particle for deliverance of a nucleic acid of interest to MSC. In view of the unpredictability of the art of delivering recombinant adenovirus *in vivo*, the lack of guidance in the instant specification and the poorly developed state of the art: undue experimentation would be required to practice the claimed methods with reasonable

expectation of success, absent a specific and detailed description in the specification. The level of skill in the art covering this invention was high at the time of invention; however, given the unpredictability of the art, the poorly developed state of the art, the lack of working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue experimentation to practice the claimed invention.

Response to Arguments- lack of enablement

Applicants traverse the claims rejection under 35 U.S.C. 112, first paragraph, on pages 7-8 of the amendment filed 3/22/04. Applicants argue that molecular cloning has become routine in the art and these aspects of the invention cannot be amount to undue experimentation. Moreover, the demonstration in cell culture that the recombinant adenoviral vector infects mesenchymal stem cells provides a person of skill in the art with the tools necessary to administer the recombinant adenovirus *in vivo*.

Applicants' arguments filed 3/22/04 have been fully considered but they are not persuasive. Applicants have argued that *in vitro* results are indicative of a successful administration of the recombinant adenovirus *in vivo*. However, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies (Kmiec, page 245, column 2). It is not clear that reliance on *in vitro* and experimental models accurately can reflect the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the *in vitro* system and the *in vivo* state. While the molecular cloning relied upon to execute the instant invention is not an unpredictable art, the generation of rAD by complex cloning techniques is a high art. The cloning techniques required to

generate the rAD did not by themselves lead to the determination that the invention would require undue experimentation. The use of the recombinant adenovirus *in vivo* would require undue experimentation in view of the unpredictability of the art of delivering recombinant adenovirus *in vivo* for therapeutic effect, the lack of guidance in the instant specification and the poorly developed state of the art.

Conclusion

Claims 54-61 are allowed.

Claim 50 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 28, 48-49 and 51-53 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

June 6, 2004

GERRY LEFFERS
PRIMARY EXAMINER